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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/142,660	12/23/98	HINTSCHE R	60953/119

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EXAMINER	
SISSON, B	
ART UNIT	**PAPER NUMBER**
1655	13

DATE MAILED: 08/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/142,660	HINTSCHE ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *08 June 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-60* is/are rejected.

7)☒ Claim(s) *58-60* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *08 June 2000* is: a)☒ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☒ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☒ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Drawings

1. The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on 8 June 2000 have been approved by the examiner.

Claim Objections

2. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. In the instant case, newly added claims 58-60 depend from newly added claim 21 yet are separated from said claim 21 by newly added independent claims 56 and 57. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for coating of an electrode with SH-biotin and detection/measurement of β-galactosidase-streptavidin wherein said β-galactosidase-streptavidin binds to the immobilized biotin and is subsequently detected by the action of β-galactosidase on ρ-aminophenol, does not reasonably provide enablement for the detection of any molecule complex in any diluent, be it in a purified state or not, and where the ultra-microelectrode array is fashioned of any material and is operated under any strength of electric field, any amplitude, and any frequency. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The amount of experimentation is great, on the order of many man-years with little if any reasonable expectation of success.

The Amount of Direction or Guidance Provided and The Presence or Absence of Working Examples

The specification has been found to provide but one example where any molecule was detected and that was for the presence of β-galactosidase-streptavidin. In accordance with the

example provided at pages 13-14 of the specification, SH-Biotin was first coated onto a gold electrode that had a width of 1 μm and an electrode spacing of 0.7 μm. The modified electrode was then dipped for 2 hours in a 50 U/ml solution of β-galactosidase-streptavidin and subsequently rinsed for 10 minutes in 0.1 mol/ml Na buffer solution.

As set forth at page 14, a Nyquist plot for a potential of 50 mV, amplitude of 10 mV and a frequency range of between $2x10^{-13}$ Hz and $1X10^{6}$ Hz, measured as two-pole impedance.

The specification does not set forth the conditions required to accurately detect any other molecule or molecule complex in any diluent under any set of conditions. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
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> *****
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> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling

> disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Claim 23 requires measurement to be made via impedance spectroscopy. However, the specification does not set forth a repeatable procedure whereby this is to be conducted. The specification does not enable the application of "a direct-current component", nor the oxidation or reduction of an electrically active molecule. Similarly, the specification does not set forth a repeatable procedure where the molecule to be detected is an antibody (claim 40) or an antigen (claim 41), nor for when the first and or second molecules comprise polynucleotides (claims 42-44). The specification has not been found to set forth a repeatable procedure whereby one of skill in the art would be able to synthesize and use an electrode fashioned of a material other than gold (claims 46-60). The limited guidance has not been found to be sufficient to enable the full scope of the claimed invention.

The Nature of the Invention

The invention relates to the detection of virtually any molecule or molecular complex, be it in a purified or heterogeneous mixture, and regardless of concentration. The claimed method employs an alternating electrical current and the skilled artisan is to measure changes in current or in electrical potential between electrode structures which are interpreted as being indicative of a molecule or molecular complex.

The State of the Prior Art

The state of the prior art in this area is relatively undeveloped, especially when one is attempting to detect any type of molecule or molecular complex, be it in a purified or heterogeneous mixture of varying concentrations, buffers, temperatures, etc.

The Relative Skill of Those in the Art

The relative skill of those in the art most closely related to the claimed invention is high, on par with those who hold a Ph.D. in biochemistry and have a firm grounding on electrical chemistries.

Response to Arguments

Applicant asserts in their response of 8 June 2000 that the specification is enabling for the claimed invention. In support of their position, applicant directs attention to new claims 21, 37 and 42 as prescribing methods enabled by the specification. As set forth at page 12, second paragraph, of the response, it is stated:

> Accordingly, Applicants believe that long as the binding creates a detectable change in current or potential, the present application provides sufficient guidance to enable a person skilled in the art to detect such binding.

This argument has been fully considered and has not been found to be persuasive towards the withdrawal of the rejection against the newly added claims. While the claims may have been tailored , they do not make up for the deficiencies of the specification. Claims alone do not enable the invention as such needs to be adequately supported in the originally filed specification. Neither the original claims, nor the original written description (specification) adequately address how one is to detect a specific molecule, or molecular complex, when any type of condition is used, or when the sample being assayed is complex and could easily give rise

to non-specific binding. In view that one is top measure changes in electric potential, any thing that changes said electrical potential would be interpreted as being an indicia of the target molecule being present. Changes in temperature, movement of non-target molecules toward or away from an electrode gap, etc., would all have an effect on electrical potential yet would give false readings of target molecule being present.

The claimed method also relates directly to performing hybridization reactions. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products. The specification of the subject application fails to take these issues into account. Similar issues surround the binding affinities between polyclonal and monoclonal antibodies and a variety of antigens. Again the specification has not been found to adequately address these issues such tat a skilled artisan would be able to practice the claimed invention to the full extent of the claims' scope sans resort to undue experimentation. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is applied anew to newly added claims 21-60.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 is indefinite with respect to what the metes and bounds of the clause: "about the size of a large molecule complex."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3592 for regular communications and (703) 308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1655

BLS
July 25, 2000